

### **REMARKS/ARGUMENTS**

Applicants and Applicants' attorneys thank Examiner Wells and Primary Examiner Padmanabhan for the courtesies extended during the telephone conference on July 29, 2003. Pursuant to 37 C.F.R. § 1.133(b), Applicants present the following statement in connection with the telephonic interview on July 29, 2003 between T. Christopher Tsang and Ann Chen, and Examiner Wells and Primary Examiner Padmanabhan:

The rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement of the test compounds were discussed. Applicants' attorneys explained that the claimed invention is directed to methods of screening for drugs based on the discovery of a novel isoform of NADH oxidase. The Examiners indicated that the rejection pertains to the scope of test agents enabled for use in the claimed methods. Applicants' attorneys responded by pointing out that use of test agents other than those disclosed in the specification is either well known in the art or requires only routine experimentation. The Examiners suggested that the claims be limited to a Markush group of test agents disclosed in the specification. Applicants' attorneys indicated that the inventors need to be consulted regarding such an amendment to the claims.

Claims 12-24 were pending in the instant application. Claims 12, 19, 22 and 24 have been amended to correct certain editorial errors. The amendment is supported by the specification as filed. No new matter has been added by these amendments.

Claims 17-24 will be pending upon entry of the above-made amendments.

#### **A. THE PRESENT INVENTION**

The present invention is based in part on the discovery of an aging-related isoform of NADH oxidase, AR-NOX. The claimed invention is directed to methods of screening agents that sequester AR-NOX by allowing a test agent to bind and/or interact with AR-NOX, and observing the outcome directly or through the use of different substrates. According to the specification at page 8, lines 7-9, and page 13, lines 16-18, an "agent that sequesters AR-NOX" refers to any molecule, compound, or treatment that interacts with AR-NOX, *i.e.*, neutralizes, binds, blocks or eliminates the AR-NOX protein, thus decreasing the reaction of AR-NOX with other substrates and inhibits the ability of AR-NOX to generate reactive

oxygen species. The test agent's ability to sequester AR-NOX is determined by basic biochemical binding assays (claim 12) and enzymatic assays (claims 17, 20 and 24).

The utility of the claimed method relates to the identification of agents that bind AR-NOX and/or modulate its activity. AR-NOX was identified in sera of aged patients which exhibited spontaneous and a much more dramatic rate of cytochrome c reduction than sera of younger subjects. This observation reasonably correlates with AR-NOX's role in oxidative changes that are associated with aging. Thus, agents identified by the claimed methods can be used to reduce the ability of AR-NOX to generate reactive oxygen species thereby reducing oxidative stress in aging.

**B. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN**

The Examiner has maintained the rejection of claims 12-24 under 35 U.S.C. § 112, first paragraph. According to the Examiner, the specification is not enabled for test agents that react with AR-NOX. The Examiner alleges that the enablement rejection is a scope of enablement rejection, wherein "test agents", other than those recited in the claims and specification, are not enabled for use in the instant method. The Examiner also alleges that because the term "test agent" encompasses every chemical possibility and NOX is present in different isoforms and hence has different chemical properties, a great amount of experimentation would be required to discover what test substances can be utilized in the instant method. The Examiner further alleges that while screening assays are well known in the art, "testing agents" that interact with AR-NOX are not. For the following reasons, Applicants respectfully traverse.

**1. The Enablement Requirement And Relevant Case Law**

The enablement requirement refers to the requirement of 35 U.S.C. § 112, first paragraph, that the specification describes (1) how to make and (2) how to use the invention. See MPEP 2164. "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." United States v. Teletronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

Where a disclosure provides considerable direction and guidance on how to practice the invention and presents working examples, and where, at the time of application, the skill in the art was quite high and the methods needed to practice the invention well known, a conclusion of enablement should be made. In re Wands, 858 F.2d 731, 740, 8 USPQ2d 1400, 1406 (Fed. Cir. 1988). The factors that are relevant in determining what constitutes undue experimentation as set forth in Wands (citing Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)) include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” Any conclusion of nonenablement must be based on the evidence as a whole, and not based on an analysis of only one of the factors while ignoring one or more of the others. In re Wands, 858 F.2d at 740, 8 USPQ2d at 1407.

## **2. The Enablement Rejection Is In Error**

In the present rejection, the Examiner alleges that the test compounds encompassed by the claimed invention have not been enabled.

In response, Applicants submit that the presently claimed invention is not directed to every possible chemical compound that binds to AR-NOX. Rather, the presently claimed invention is directed to screening methods useful for the identification from a collection of test agents with previously unknown activity only those agents that sequester AR-NOX. Specifically, the presently claimed methods relate to the use of basic biochemical binding assays and enzymatic assay to determine whether a test agent binds and/or interacts with AR-NOX. The presently claimed invention is neither directed to test agents *per se* nor directed to methods of using the identified test agents.

Applicants point out that the Examiner has not made an enablement rejection over the method *as a whole*. “The invention that one skilled in the art must be enabled to make and use is *that defined by the claim(s)* of the particular application or patent.” See MPEP 2164 (emphasis added). An enabling description for a process or method requires sufficient disclosure as to “how to carry out *the claimed process*.” In re Barrett, 440 F.2d 1391, 1392 (CCPA 1971) (emphasis added).

The Examiner also alleges that while screening assays are well known in the art, “testing agents” that interact with AR-NOX are not. Applicants point out that the Examiner seems to admit that the manipulations involved in screening assays are well known in the art, and if so, the specification meets the enablement requirement. In this statement, what concerns the Examiner appears to be the knowledge of the results of the claimed method where different classes of test agents are used. Applicants submit that it is irrelevant to the enablement of the claimed method whether testing agents that interact with AR-NOX are well known or are not well known. To “screen” means “to select or eliminate by a selection process.”<sup>1</sup> The novelty of the invention lies in the use of novel AR-NOX protein to select agents that interact with it and that may be developed as a therapeutic agent.

Applicants respectfully submit that the enablement rejection has been issued in error.

**a. The Specification Enables One Skilled In the Art To Make The Test Agents Used In The Claimed Methods**

In the present case, as discussed above, the specification enables one of skill in the art to make and use any test agents in the claimed methods. As a starting material in the claimed methods, the test agents, which can be a drug, an antibiotic, an enzyme, a chemical compound, a mixture of chemical compounds, a member of a chemical (*e.g.*, combinatorial) library, a biological macromolecule, and analogues thereof, are readily available to one skilled in the art.

Applicants submit that the presently claimed invention relates to screening methods, the utility and commercial value of which lie in their abilities to screen a wide variety of agents and determine which agent interacts with the substance of interest, *i.e.*, AR-NOX. Applicants point out that the skill in the fields of biochemistry and drug screening technology is high and the number of chemical compounds (typically organized in libraries) that are available is abundant and growing. Therefore, it is unnecessary and impractical for Applicants to recite every single possible agent for use in said screening method.

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<sup>1</sup> Merriam-Webster's Collegiate Dictionary (11th ed. 2003).

The term “test agent”<sup>2</sup> as used in the claimed methods refers to a substance that is to be screened by one or more of the claimed assays. The test agent can be any chemical molecule or compound that one reasonably skilled in the art would use in a screening method as described. See specification, page 8, lines 7-8. Such agents, as understood by one of ordinary skill in the art, can be a drug, an antibiotic, an enzyme, a chemical compound, a mixture of chemical compounds, a member of a chemical (*e.g.*, combinatorial) library, a biological macromolecule, and analogues thereof. Examples of possible test agents described in the specification as originally filed include, but are not limited to, ubiquinone (page 1, lines 13-14; page 7, lines 11-13), antibodies (page 14, lines 4-6), those selected from a combinatorial chemistry library (page 16, lines 13-16), and proteins (page 16, lines 31-32).

Applicants respectfully point out that the above-described test agents are commonly available from many sources. For example, Sigma-Aldrich (St. Louis, MO) provides a number of combinatorial chemistry libraries and compound libraries for assay validation and high throughput screening. Exhibit 1 as attached hereto is a computer print-out from Sigma-Aldrich’s website that describes CombiKits™ combinatorial chemistry library of carboxylic acids, arylboronic acids, amines, alcohols, isocyanates; LOPAC™ Library of Pharmacologically-Active Compounds; LIGAND-SETS™ libraries of small organic ligands; and Aldrich Library of Rare Chemicals of more than 100,000 small-molecule compounds, including plant extracts and microbial cultures, all of which can be used as test agents in screening assays. One of ordinary skill in the art can purchase any one of the above-mentioned libraries, follow the steps recited in the claimed assays, and determine whether a test agent in these libraries is an “agent that sequester AR-NOX” without undue experimentation.

Additionally, many of these test agents are also well known in the art. For instance, antibodies that bind and/or interact with AR-NOX can also be prepared using a wide variety of techniques known in the art. Another example is coenzyme Q (ubiquinone) which is naturally occurring and can be isolated from many sources. It can also be purchased from

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<sup>2</sup> An “agent”, as understood by one of ordinary skill in the art, can mean “[a] force or substance that causes a change”, “something that produces or is capable of producing an effect,” or “a chemically, physically, or biologically active principle.” See The American Heritage College Dictionary (3d ed. 1997); and Merriam-Webster’s Collegiate Dictionary (11th ed. 2003).

health food stores or chemical supply companies such as Sigma-Aldrich. Derivatives of ubiquinone can be readily synthesized by one of ordinary skill in the art. A patent need not teach, and preferably omits, what is well known in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied; 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Accordingly, Applicants submit that the test agents for use in the claimed screening methods are enabled in the specification.

**b. The Specification Enables One of Ordinary Skill In the Art To Use The Test Agents In The Claimed Methods**

Claim 12 recites a method of screening for agents that bind AR-NOX by measuring the formation of a complex comprising AR-NOX and the test agent. Simply put, claim 12 recites a basic biochemical binding assay for identifying those test agents that bind AR-NOX.

The binding interaction between AR-NOX and the test agent can be measured in a variety of ways known in the art. The specification describes some examples including labeling or separation which are useful in determining whether the test agent binds to AR-NOX. See specification, page 15, line 16 to page 16, line 12.

In one embodiment, the test agent may be labeled with a radioactive isotope while AR-NOX can be immobilized on a solid phase prior to the binding reaction, and unbound labeled test agents can be removed after the binding reaction by washing the solid phase. See specification, page 15, lines 24-34. In another embodiment, if there is a size difference between the labeled test agent and the unlabeled AR-NOX, separation can be achieved by passing the products of the binding reaction through an ultrafilter whose pores allow passage of unbound labeled test agents but not of the unbound AR-NOX or of labeled test agents bound to AR-NOX. See specification, page 16, lines 5-9.

Claims 17, 20 and 24 recite methods of screening for agents that decrease the reaction of AR-NOX with its substrates. Simply put, claims 17, 20 and 24 recites the use of enzymatic assays to identify those test agents that interact with AR-NOX.

Specifically, claim 17 recites a method of screening for agents that affects the ability of AR-NOX to reduce cytochrome c in the presence of a substrate that generates reactive oxygen species. Cytochrome c reduction can be measured, for example, by

spectrophotometric absorbance at 540 nm to 550 nm. See specification, page 14, lines 13-14; page 24, line 36 to page 25, line 2; and claim 19.

Claim 20 recites a method of screening for agents that affect the ability of AR-NOX to reduce a substrate such as ascorbate radical (page 14, line 16) and NAD<sup>+</sup> (page 14, line 19). Ascorbate radical reduction and NAD<sup>+</sup> reduction can be measured by spectrophotometric absorbance at 265 nm and at 340 nm, respectively. See specification, page 14, lines 15-18 and claim 22; and page 8, lines 33-35 and page 24, lines 24-26, respectively.

Claim 24 recites a method of screening for agents that affect the disulfide-thiol interchange activity of AR-NOX. The disulfide-thiol interchange activity can be measured using dithio-dipyridyl substrates. See specification, page 15, lines 3-7.

Applicants submit that one skilled in the art would know how to effectively incubate a test agent with AR-NOX. The skilled person would also understand the basic principles of spectrophotometry and know how to analyze a sample's absorbance spectrum. Applicants further submit that one skilled in the art would know how to use dithio-dipyridyl substrates as taught in Morr   et al., *Mol Cell Biochem.* 1999 Oct;200(1-2):7-13, which is incorporated at page 15, lines 6-7 of the specification as originally filed. Based on such disclosures and knowledge in the art, no undue experimentation is required to carry out the claimed invention.

The Examiner alleges that the enablement rejection is a scope of enablement rejection, wherein "test agents", other than those recited in the claims and specification, are not enabled for use in the instant method. Applicants submit that even if test agents other than those disclosed in the specification are used, only routine experimentation is required to carry out the incubation and detection steps. As discussed above, the binding interaction between AR-NOX and any test agent can be measured in a variety of ways known in the art.

The specification need only be reasonable with respect to the art involved; they need not inform the layman nor disclose what the skilled already possess. General Electric Co. v. Brenner, 159 USPQ 335, 337 (D.C. Cir. 1968). Thus, Applicants submit that the term "test agent" as used in the claimed methods is generic and should not be limited to those specifically recited in the specification. Accordingly, the specification enables one skilled in the art as to how to use the test agents in the claimed assays. As long as the specification discloses at least one method for making and using the claimed invention that bears a

reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In sum, Applicants submit that the specification enables one of ordinary skill in the art to make and use any test agents (*e.g.*, small molecules, chemical compounds, peptides and proteins, etc.) in the biochemical binding assay and enzymatic assay of the claimed methods. The rejection should be withdrawn.

**CONCLUSION**

In light of the submissions herewith, the above remarks and amendments, it is submitted that all outstanding rejections are obviated and should be withdrawn. Attorneys for Applicants respectfully submit that the pending claims fully meet all statutory requirements for patentability. Withdrawal of the rejections and allowance is respectfully requested.

If any issues remain, it is requested that the undersigned be contacted by telephone to discuss same.

Respectfully submitted,

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